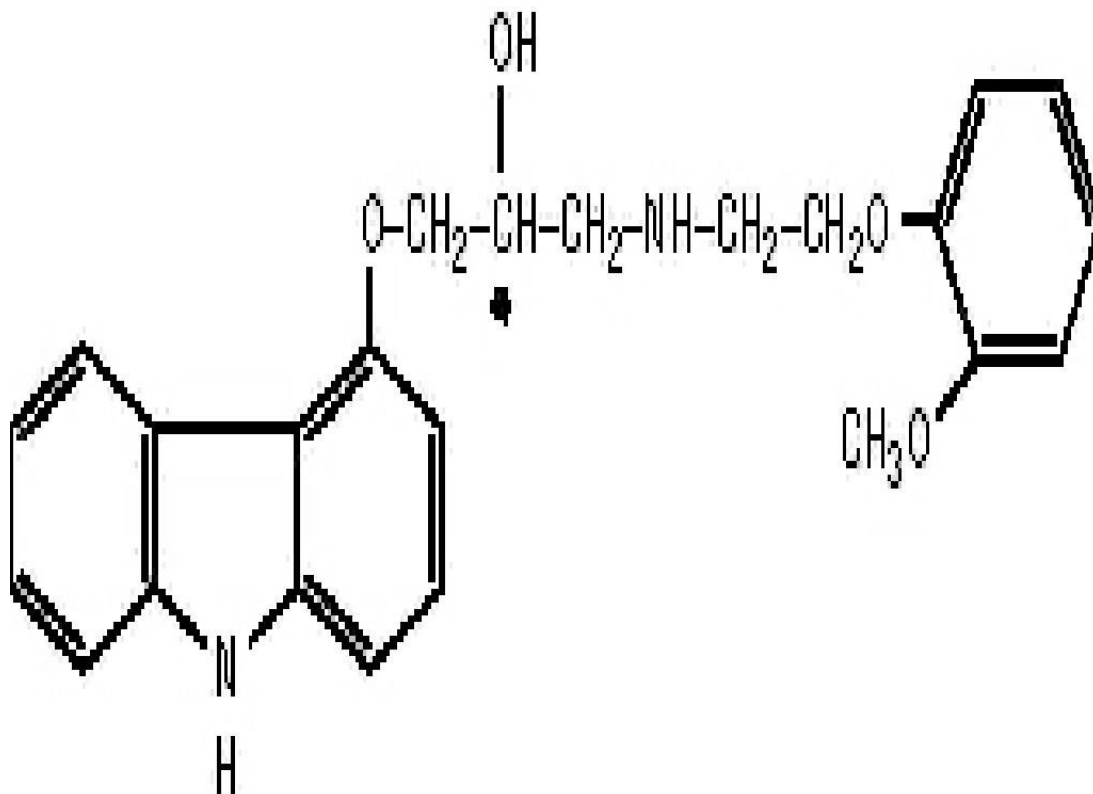


**CARVEDILOL - carvedilol tablet**  
**REMEDYREPACK INC.**

**DESCRIPTION**

Carvedilol is a nonselective blocking agent with activity. It is (Carvedilol is a racemic mixture with the following structure:



COREG is a white, oval, film-coated tablet containing 3.125 mg, 6.25 mg, 12.5 mg, or 25 mg of carvedilol. The 6.25 mg, 12.5 mg, and 25 mg tablets are TILTAB tablets. Inactive ingredients consist of colloidal silicon dioxide, crospovidone, hypromellose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sucrose, and titanium dioxide.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

COREG is a racemic mixture in which nonselective blocking activity is present in the S(-) enantiomer and blocking activity is present in both R(+) and S(-) enantiomers at equal potency. COREG has no intrinsic sympathomimetic activity.

**PHARMACODYNAMICS**

**Heart Failure**

The basis for the beneficial effects of COREG in heart failure is not established.

Two placebo-controlled studies compared the acute hemodynamic effects of COREG to baseline measurements in 59 and 49 patients with NYHA class II-IV heart failure receiving diuretics, ACE inhibitors, and digitalis. There were significant reductions in systemic blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and heart rate. Initial effects on cardiac output, stroke volume index, and systemic vascular resistance were small and variable.

These studies measured hemodynamic effects again at 12 to 14 weeks. COREG significantly reduced systemic blood pressure, pulmonary artery pressure, right atrial pressure, systemic vascular resistance,

and heart rate, while stroke volume index was increased.

#### Left Ventricular Dysfunction Following Myocardial Infarction

The basis for the beneficial effects of COREG in patients with left ventricular dysfunction following an acute myocardial infarction is not established.

#### Hypertension

The mechanism by which produces an antihypertensive effect has not been established. blocking effect is usually seen within 1 hour of drug administration.

Due to the blocking activity of carvedilol, blood pressure is lowered more in the standing than in the supine position, and symptoms of postural hypotension (1.8 percent), including rare instances of syncope, can occur. Following oral administration, when postural hypotension has occurred, it has been transient and is uncommon when COREG is administered with food at the recommended starting dose and titration increments are closely followed [see Dosage and Administration].

In hypertensive patients with normal renal function, therapeutic doses of COREG decreased renal vascular resistance with no change in glomerular filtration rate or renal plasma flow. Changes in excretion of sodium, potassium, uric acid, and phosphorus in hypertensive patients with normal renal function were similar after COREG and placebo.

COREG has little effect on plasma catecholamines, plasma aldosterone, or electrolyte levels, but it does significantly reduce plasma renin activity when given for at least 4 weeks. It also increases levels of atrial natriuretic peptide.

#### PHARMACOKINETICS

COREG is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25 percent to 35 percent due to a significant degree of first-pass metabolism.

Following oral administration, the apparent mean terminal elimination half-life of carvedilol generally ranges from 7 to 10 hours. Plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability. Taking COREG with food should minimize the risk of orthostatic hypotension.

Carvedilol is extensively metabolized. Following oral administration of radiolabelled carvedilol to healthy volunteers, carvedilol accounted for only about 7 percent of the total radioactivity in plasma as measured by area under the curve (AUC). Less than 2 percent of the dose was excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile into the feces. Demethylation and hydroxylation at the phenol ring produce 3 active metabolites with blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for

Compared to carvedilol, the 3 active metabolites exhibit weak vasodilating activity. Plasma concentrations of the active metabolites are about one-tenth of those observed for carvedilol and have pharmacokinetics similar to the parent.

Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R(+)-carvedilol approximately 2 to 3 times higher than S(-)-carvedilol following oral administration in healthy subjects. The mean apparent terminal elimination half-lives for R(+)-carvedilol range from 5 to 9 hours compared with 7 to 11 hours for the S(-)-enantiomer.

The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and 5'-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary importance in the O-methylation pathway of S(-)-carvedilol.

Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared to extensive metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only about 20 percent to 25 percent in poor metabolizers, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol. The pharmacokinetics of carvedilol do not appear to be different in poor metabolizers of S-mephenytoin (patients deficient in cytochrome P450 2C19).

Carvedilol is more than 98 percent bound to plasma proteins, primarily with albumin. The plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol is a basic, lipophilic compound with a steady-state volume of distribution of approximately 115 L, indicating substantial distribution into extravascular tissues. Plasma clearance ranges from 500 to 700 mL/min.

## USE IN SPECIFIC POPULATIONS

### Heart Failure

Steady-state plasma concentrations of carvedilol and its enantiomers increased proportionally over the 6.25 to 50 mg dose range in patients with heart failure. Compared to healthy subjects, heart failure patients had increased mean AUC and C<sub>max</sub> values for carvedilol and its enantiomers, with up to 50 percent to 100 percent higher values observed in 6 patients with NYHA class IV heart failure. The mean apparent terminal elimination half-life for carvedilol was similar to that observed in healthy subjects.

### Geriatric

Plasma levels of carvedilol average about 50% higher in the elderly compared to young subjects.

### Hepatic Impairment

Compared to healthy subjects, patients with severe liver impairment (cirrhosis) exhibit a 4- to 7-fold increase in carvedilol levels. Carvedilol is contraindicated in patients with severe liver impairment.

### Renal Impairment

Although carvedilol is metabolized primarily by the liver, plasma concentrations of carvedilol have been reported to be increased in patients with renal impairment. Based on mean AUC data, approximately 40 percent to 50 percent higher plasma concentrations of carvedilol were observed in hypertensive patients with moderate to severe renal impairment compared to a control group of hypertensive patients with normal renal function. However, the ranges of AUC values were similar for both groups. Changes in mean peak plasma levels were less pronounced, approximately 12 percent to 26 percent higher in patients with impaired renal function.

Consistent with its high degree of plasma protein-binding, carvedilol does not appear to be cleared significantly by hemodialysis.

### Drug-Drug Interactions

Since carvedilol undergoes substantial oxidative metabolism, the metabolism and pharmacokinetics of carvedilol may be affected by induction or inhibition of cytochrome P450 enzymes.

### Amiodarone

In a pharmacokinetic study conducted in 106 Japanese patients with heart failure, coadministration of small loading and maintenance doses of amiodarone with carvedilol resulted in at least a 2-fold increase in the steady-state trough concentrations of S(-)-carvedilol [see Drug Interactions].

### Cimetidine

In a pharmacokinetic study conducted in 10 healthy male subjects, cimetidine (1,000 mg/day) increased the steady-state AUC of carvedilol by 30 percent with no change in C<sub>max</sub> [see Drug Interactions].

### Digoxin

Following concomitant administration of carvedilol (25 mg once daily) and digoxin (0.25 mg once daily) for 14 days, steady-state AUC and trough concentrations of digoxin were increased by 14 percent and 16 percent, respectively, in 12 hypertensive patients [see Drug Interactions].

### Glyburide

In 12 healthy subjects, combined administration of carvedilol (25 mg once daily) and a single dose of glyburide did not result in a clinically relevant pharmacokinetic interaction for either compound.

### Hydrochlorothiazide

A single oral dose of carvedilol 25 mg did not alter the pharmacokinetics of a single oral dose of hydrochlorothiazide 25 mg in 12 patients with hypertension. Likewise, hydrochlorothiazide had no effect on the pharmacokinetics of carvedilol.

### Rifampin

In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin (600 mg daily for 12 days) decreased the AUC and Cmax of carvedilol by about 70 percent [see Drug Interactions].

#### Torsemide

In a study of 12 healthy subjects, combined oral administration of carvedilol 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant differences in their pharmacokinetics compared with administration of the drugs alone.

#### Warfarin

Carvedilol (12.5 mg twice daily) did not have an effect on the steady-state prothrombin time ratios and did not alter the pharmacokinetics of R(+)- and S(-)-warfarin following concomitant administration with warfarin in 9 healthy volunteers.

## INDICATIONS & USAGE

### Heart Failure

COREG is indicated for the treatment of mild-to-severe chronic heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors, and digitalis, to increase survival and, also, to reduce the risk of hospitalization [see Drug Interactions and Clinical Studies].

### Left Ventricular Dysfunction Following Myocardial Infarction

COREG is indicated to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of greater than 40 percent (with or without symptomatic heart failure) [see Clinical Studies].

### Hypertension

COREG is indicated for the management of essential hypertension [see Clinical Studies]. It can be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics [see Drug Interactions].

## CONTRAINDICATIONS

COREG is contraindicated in the following conditions:

- Bronchial asthma or related bronchospastic conditions. Deaths from status asthmaticus have been reported following single doses of COREG.
- Second- or third-degree AV block
- Sick sinus syndrome
- Severe bradycardia (unless a permanent pacemaker is in place)
- Patients with cardiogenic shock or who have decompensated heart failure requiring the use of intravenous inotropic therapy. Such patients should first be weaned from intravenous therapy before initiating COREG.
- Patients with severe hepatic impairment
- Patients with a history of a serious hypersensitivity reaction (e.g., Stevens-Johnson syndrome, anaphylactic reaction, angioedema) to any component of this medication or other medications containing carvedilol.
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## WARNINGS AND PRECAUTIONS

### Cessation of Therapy

Patients with coronary artery disease, who are being treated with COREG, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with COREG. The last 2 complications may occur with or without preceding exacerbation of the angina pectoris. As with other when discontinuation of COREG is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. COREG should be discontinued over 1 to 2 weeks whenever possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that COREG be promptly reinstituted, at least temporarily.

Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue therapy with COREG abruptly even in patients treated only for hypertension or heart failure.

#### Bradycardia

In clinical trials, COREG caused bradycardia in about 2 percent of hypertensive patients, 9 percent of heart failure patients, and 6.5 percent of myocardial infarction patients with left ventricular dysfunction. If pulse rate drops below 55 beats/minute, the dosage should be reduced.

#### Hypotension

In clinical trials of primarily mild-to-moderate heart failure, hypotension and postural hypotension occurred in 9.7 percent and syncope in 3.4 percent of patients receiving COREG compared to 3.6 percent and 2.5 percent of placebo patients, respectively. The risk for these events was highest during the first 30 days of dosing, corresponding to the up-titration period and was a cause for discontinuation of therapy in 0.7 percent of patients receiving COREG, compared to 0.4 percent of placebo patients. In a long-term, placebo-controlled trial in severe heart failure (COPERNICUS), hypotension and postural hypotension occurred in 15.1 percent and syncope in 2.9 percent of heart failure patients receiving COREG compared to 8.7 percent and 2.3 percent of placebo patients, respectively. These events were a cause for discontinuation of therapy in 1.1 percent of patients receiving COREG, compared to 0.8 percent of placebo patients.

Postural hypotension occurred in 1.8 percent and syncope in 0.1 percent of hypertensive patients, primarily following the initial dose or at the time of dose increase and was a cause for discontinuation of therapy in 1 percent of patients.

In the CAPRICORN study of survivors of an acute myocardial infarction, hypotension or postural hypotension occurred in 20.2 percent of patients receiving COREG compared to 12.6 percent of placebo patients. Syncope was reported in 3.9 percent and 1.9 percent of patients, respectively. These events were a cause for discontinuation of therapy in 2.5 percent of patients receiving COREG, compared to 0.2 percent of placebo patients.

Starting with a low dose, administration with food, and gradual up-titration should decrease the likelihood of syncope or excessive hypotension [see Dosage and Administration]. During initiation of therapy, the patient should be cautioned to avoid situations such as driving or hazardous tasks, where injury could result should syncope occur.

#### Heart Failure/Fluid Retention

Worsening heart failure or fluid retention may occur during up-titration of carvedilol. If such symptoms occur, diuretics should be increased and the carvedilol dose should not be advanced until clinical stability resumes [see Dosage and Administration]. Occasionally it is necessary to lower the carvedilol dose or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of, or a favorable response to, carvedilol. In a placebo-controlled trial of patients with severe heart failure, worsening heart failure during the first 3 months was reported to a similar degree with carvedilol and with placebo. When treatment was maintained beyond 3 months, worsening heart failure was reported less frequently in patients treated with carvedilol than with placebo. Worsening heart failure observed during long-term therapy is more likely to be related to the patients' underlying disease than to treatment with carvedilol.

#### Non-allergic Bronchospasm

Patients with bronchospastic disease (e.g., chronic bronchitis and emphysema) should, in general, not receive COREG. COREG may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if COREG is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous is minimized.

In clinical trials of patients with heart failure, patients with bronchospastic disease were enrolled if they did not require oral or inhaled medication to treat their bronchospastic disease. In such patients, it is recommended that carvedilol be used with caution. The dosing recommendations should be followed closely and the dose should be lowered if any evidence of bronchospasm is observed during up-titration.

#### Glycemic Control in Type 2 Diabetes

In general, may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned about these possibilities.

In heart failure patients with diabetes, carvedilol therapy may lead to worsening hyperglycemia, which responds to intensification of hypoglycemic therapy. It is recommended that blood glucose be monitored when carvedilol dosing is initiated, adjusted, or discontinued. Studies designed to examine the effects of carvedilol on glycemic control in patients with diabetes and heart failure have not been conducted.

In a study designed to examine the effects of carvedilol on glycemic control in a population with mild-to-moderate hypertension and well-controlled type 2 diabetes mellitus, carvedilol had no adverse effect on glycemic control, based on HbA1c measurements [see Clinical Studies].

#### Peripheral Vascular Disease

can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

#### Deterioration of Renal Function

Rarely, use of carvedilol in patients with heart failure has resulted in deterioration of renal function. Patients at risk appear to be those with low blood pressure (systolic blood pressure greater than 100

mm Hg), ischemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency. Renal function has returned to baseline when carvedilol was stopped. In patients with these risk factors it is recommended that renal function be monitored during up-titration of carvedilol and the drug discontinued or dosage reduced if worsening of renal function occurs.

#### Anesthesia and Major Surgery

If treatment with COREG is to be continued perioperatively, particular care should be taken when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used [see Overdosage for information on treatment of bradycardia and hypertension].

#### Thyrotoxicosis

blockade may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.

#### Pheochromocytoma

In patients with pheochromocytoma, an agent should be initiated prior to the use of any agent. Although carvedilol has both pharmacologic activities, there has been no experience with its use in this condition. Therefore, caution should be taken in the administration of carvedilol to patients suspected of having pheochromocytoma.

#### Prinzmetal's Variant Angina

Agents with non-selective activity may provoke chest pain in patients with Prinzmetal's variant angina. There has been no clinical experience with carvedilol in these patients although the activity may prevent such symptoms. However, caution should be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

#### Risk of Anaphylactic Reaction

While taking patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

## DRUG INTERACTIONS

#### CYP2D6 Inhibitors and Poor Metabolizers

Interactions of carvedilol with potent inhibitors of CYP2D6 isoenzyme (such as quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be expected to increase blood levels of the R(+) enantiomer of carvedilol [see Clinical Pharmacology]. Retrospective analysis of side effects in clinical trials showed that poor 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the R(+) enantiomer.

#### Hypotensive Agents

Patients taking both agents with properties and a drug that can deplete catecholamines (e.g., reserpine and monoamine oxidase inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia.

Concomitant administration of clonidine with agents with properties may potentiate blood-pressure- and heart-rate-lowering effects. When concomitant treatment with agents with properties and clonidine is to be terminated, the agent should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.

#### Cyclosporine

Modest increases in mean trough cyclosporine concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30 percent of patients, the dose of cyclosporine had to be reduced in order to maintain cyclosporine concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporine was reduced about 20 percent in these patients. Due to wide interindividual variability in the dose adjustment required, it is recommended that cyclosporine concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporine be adjusted as appropriate.

#### Digitalis Glycosides

Both digitalis glycosides and slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. Digoxin concentrations are increased by about 15 percent when digoxin and carvedilol are administered concomitantly. Therefore, increased monitoring of digoxin is recommended when initiating, adjusting, or discontinuing COREG [see Clinical Pharmacology].

#### Inducers/Inhibitors of Hepatic Metabolism

Rifampin reduced plasma concentrations of carvedilol by about 70 percent [see Clinical Pharmacology].

Cimetidine increased AUC by about 30 percent but caused no change in C<sub>max</sub> [see Clinical Pharmacology].

#### Amiodarone

Amiodarone, and its metabolite desethyl amiodarone, inhibitors of CYP2C9 and P-glycoprotein, increased concentrations of the S(-)-enantiomer of carvedilol by at least 2-fold [see Clinical Pharmacology]. The concomitant administration of amiodarone or other CYP2C9 inhibitors such as fluconazole with COREG may enhance the properties of carvedilol resulting in further slowing of the heart rate or cardiac conduction. Patients should be observed for signs of bradycardia or heart block,

particularly when one agent is added to pre-existing treatment with the other.

#### Calcium Channel Blockers

Conduction disturbance (rarely with hemodynamic compromise) has been observed when COREG is co-administered with diltiazem. As with other agents with properties, if COREG is to be administered with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

#### Insulin or Oral Hypoglycemics

Agents with properties may enhance the blood-sugar-reducing effect of insulin and oral hypoglycemics. Therefore, in patients taking insulin or oral hypoglycemics, regular monitoring of blood glucose is recommended [see Warnings and Precautions].

## PREGNANCY

Pregnancy Category C. Studies performed in pregnant rats and rabbits given carvedilol revealed increase post-implantation loss in rats at doses of 300 mg/kg/day (50 times the recommended human dose [MRHD] as mg/m<sup>2</sup>) and in rabbits at doses of 75 mg/kg/day (25 times the MRHD as mg/m<sup>2</sup>). In the rates, there was also a decrease in fetal body weight at the maternally toxic dose of 300 mg/kg/day (50 times the MRHD as mg/m<sup>2</sup>), which was accompanied by an elevation in the frequency of fetuses with delayed skeletal development (missing or stunted 13th rib). In rates the no-observed-effect level for developmental toxicity was 60 mg/kg/day (10 times the MRHD as mg/m<sup>2</sup>); in rabbits it was 15 mg/kg/day (5 times the MRHD as mg/m<sup>2</sup>). There are no adequate and well-controlled studies in pregnant women. COREG should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

## NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Studies in rats have shown that carvedilol and/or its metabolites (as well as other cross the placental barrier and are excreted in breast milk. There was increased mortality at one week post-partum in neonates from rats treated with 60 mg/kg/day (10 times the MRHD as mg/m<sup>2</sup>) and above during the last trimester through day 22 of lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from especially bradycardia, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. The effects of other agents have included perinatal and neonatal distress.

## PEDIATRIC USE

Effectiveness of COREG in patients younger than 18 years of age has not been established.

## GERIATRIC USE

Of the 765 patients with heart failure randomized to COREG in US clinical trials, 31 percent (235) were 65 years of age or older, and 7.3 percent (56) were 75 years of age or older. Of the 1,156 patients randomized to COREG in a long-term, placebo-controlled trial in severe heart failure, 47 percent (547) were 65 years of age or older, and 15 percent (174) were 75 years of age or older. Of 3,025 patients receiving COREG in heart failure trials worldwide, 42 percent were 65 years of age or older.

Of the 975 myocardial infarction patients randomized to COREG in the CAPRICORN trial, 48 percent (468) were 65 years of age or older, and 11 percent (111) were 75 years of age or older.

Of the 2,065 hypertensive patients in US clinical trials of efficacy or safety who were treated with COREG, 21 percent (436) were 65 years of age or older. Of 3,722 patients receiving COREG in hypertension clinical trials conducted worldwide, 24 percent were 65 years of age or older.

With the exception of dizziness in hypertensive patients (incidence 8.8 percent in the elderly versus 6% in younger patients), no overall differences in the safety or effectiveness (see Figures 2 and 4) were observed between the older subjects and younger subjects in each of these populations. Similarly, other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

## ADVERSE REACTIONS

### Clinical Studies Experience

COREG has been evaluated for safety in patients with heart failure (mild, moderate, and severe), in patients with left ventricular dysfunction following myocardial infarction and in hypertensive patients. The observed adverse event profile was consistent with the pharmacology of the drug and the health status of the patients in the clinical trials. Adverse events reported for each of these patient populations are provided below. Excluded are adverse events considered too general to be informative, and those

not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population. Rates of adverse events were generally similar across demographic subsets (men and women, elderly and non-elderly, blacks and non-blacks).

#### Heart Failure

COREG has been evaluated for safety in heart failure in more than 4,500 patients worldwide of whom more than 2,100 participated in placebo-controlled clinical trials. Approximately 60 percent of the total treated population in placebo-controlled clinical trials received COREG for at least 6 months and 30 percent received COREG for at least 12 months. In the COMET trial, 1,511 patients with mild-to-moderate heart failure were treated with COREG for up to 5.9 years (mean 4.8 years). Both in US clinical trials in mild-to-moderate heart failure that compared COREG in daily doses up to 100 mg (n = 765) to placebo (n = 437), and in a multinational clinical trial in severe heart failure (COPERNICUS) that compared COREG in daily doses up to 50 mg (n = 1,156) with placebo (n = 1,133), discontinuation rates for adverse experiences were similar in carvedilol and placebo patients. In placebo-controlled clinical trials, the only cause of discontinuation less than 1 percent, and occurring more often on carvedilol was dizziness (1.3 percent on carvedilol, 0.6 percent on placebo in the COPERNICUS trial).

Table 1 shows adverse events reported in patients with mild-to-moderate heart failure enrolled in US placebo-controlled clinical trials, and with severe heart failure enrolled in the COPERNICUS trial. Shown are adverse events that occurred more frequently in drug-treated patients than placebo-treated patients with an incidence of less than 3 percent in patients treated with carvedilol regardless of causality. Median study medication exposure was 6.3 months for both carvedilol and placebo patients in the trials of mild-to-moderate heart failure, and 10.4 months in the trial of severe heart failure patients. The adverse event profile of COREG observed in the long-term COMET study was generally similar to that observed in the US Heart Failure Trials.

Table 1. Adverse Events (percent) Occurring More Frequently With COREG Than With Placebo in Patients With Mild-to-Moderate Heart Failure (HF) Enrolled in US Heart Failure Trials or in Patients With Severe Heart Failure in the COPERNICUS Trial (Incidence greater than 3 percent in Patients Treated With Carvedilol, Regardless of Causality)

Mild-to-Moderate HF	Severe HF	COREG	Placebo	COREG	Placebo	(n = 765)	(n = 437)	(n = 1,156)	(n = 1,133)
Body as a Whole	Asthenia	77	11	9	3				
Fatigue	24	22	1						
Digoxin level increased	54	21							
Edema generalized	53	65							
Edema dependent	42								
Cardiovascular	Bradycardia	91	103						
Hypotension	93	148							
Syncope	33	85							
Angina pectoris	23	64							
Central Nervous System	Dizziness	32	19	24	17				
Headache	87	53							
Gastrointestinal	Diarrhea	126	53						
Nausea	95	43							
Vomiting	64	12							
Metabolic	Hyperglycemia	128	53						
Weight increase	107	121	11						
BUN increased	65								
NPN increased	65								
Hypercholesterolemia	43	11							
Edema peripheral	21	76							
Musculoskeletal	Arthralgia	65	11						
Respiratory	Cough increased	89	54						
Rales	44	2							
Vision	Vision abnormal	52							

Cardiac failure and dyspnea were also reported in these studies, but the rates were equal or greater in patients who received placebo.

The following adverse events were reported with a frequency of less than 1 percent but greater than 3 percent and more frequently with COREG in either the US placebo-controlled trials in patients with mild-to-moderate heart failure, or in patients with severe heart failure in the COPERNICUS trial.

Incidence less than 1 percent to greater than 3 percent

Body as a Whole: Allergy, malaise, hypovolemia, fever, leg edema.

Cardiovascular: Fluid overload, postural hypotension, aggravated angina pectoris, AV block, palpitation, hypertension.

Central and Peripheral Nervous System: Hypesthesia, vertigo, paresthesia.

Gastrointestinal: Melena, periodontitis.

Liver and Biliary System: SGPT increased, SGOT increased.

Metabolic and Nutritional: Hyperuricemia, hypoglycemia, hyponatremia, increased alkaline phosphatase, glycosuria, hypervolemia, diabetes mellitus, GGT increased, weight loss, hyperkalemia, creatinine increased.

Musculoskeletal: Muscle cramps.

Platelet, Bleeding and Clotting: Prothrombin decreased, purpura, thrombocytopenia.

Psychiatric: Somnolence.

Reproductive, male: Impotence.

Special Senses: Blurred vision.

Urinary System: Renal insufficiency, albuminuria, hematuria.

#### Left Ventricular Dysfunction Following Myocardial Infarction

COREG has been evaluated for safety in survivors of an acute myocardial infarction with left ventricular dysfunction in the CAPRICORN trial which involved 969 patients who received COREG and 980 who received placebo. Approximately 75 percent of the patients received COREG for at least 6 months and 53 percent received COREG for at least 12 months. Patients were treated for an average of 12.9 months and 12.8 months with COREG and placebo, respectively.

The most common adverse events reported with COREG in the CAPRICORN trial were consistent with the profile of the drug in the US heart failure trials and the COPERNICUS trial. The only additional adverse events reported in CAPRICORN in less than 3 percent of the patients and more commonly on carvedilol were dyspnea, anemia, and lung edema. The following adverse events were reported with a frequency of less than 1 percent but greater than 3 percent and more frequently with COREG: Flu syndrome, cerebrovascular accident, peripheral vascular disorder, hypotonia, depression,



gastrointestinal pain, arthritis, and gout. The overall rates of discontinuations due to adverse events were similar in both groups of patients. In this database, the only cause of discontinuation less than 1 percent, and occurring more often on carvedilol was hypotension (1.5 percent on carvedilol, 0.2 percent on placebo).

#### Hypertension

COREG has been evaluated for safety in hypertension in more than 2,193 patients in US clinical trials and in 2,976 patients in international clinical trials. Approximately 36 percent of the total treated population received COREG for at least 6 months. Most adverse events reported during therapy with COREG were of mild to moderate severity. In US controlled clinical trials directly comparing COREG in doses up to 50 mg (n = 1,142) to placebo (n = 462), 4.9 percent of patients receiving COREG discontinued for adverse events versus 5.2 percent of placebo patients. Although there was no overall difference in discontinuation rates, discontinuations were more common in the carvedilol group for postural hypotension (1 percent versus 0). The overall incidence of adverse events in US placebo-controlled trials increased with increasing dose of COREG. For individual adverse events this could only be distinguished for dizziness, which increased in frequency from 2 percent to 5 percent as total daily dose increased from 6.25 mg to 50 mg.

Table 2 shows adverse events in US placebo-controlled clinical trials for hypertension that occurred with an incidence of less than 1 percent regardless of causality, and that were more frequent in drug-treated patients than placebo-treated patients.

Table 2. Adverse Events (percent) Occurring in US Placebo-Controlled Hypertension Trials (Incidence less than 1 percent, Regardless of Causality)

COREG	Placebo (n = 1,142)	(n = 462)	Cardiovascular	Bradycardia	2	Postural hypotension	2	Peripheral edema	1	Central Nervous System	Dizziness	6	Insomnia	2	Gastrointestinal	Diarrhea	2	Hematologic	Thrombocytopenia	1	Metabolic	Hypertriglyceridemia	1	Shown

are events with rate less than 1 percent rounded to nearest integer.

Dyspnea and fatigue were also reported in these studies, but the rates were equal or greater in patients who received placebo.

The following adverse events not described above were reported as possibly or probably related to COREG in worldwide open or controlled trials with COREG in patients with hypertension or heart failure.

Incidence less than 0.1 percent to greater than 1 percent

Cardiovascular: Peripheral ischemia, tachycardia.

Central and Peripheral Nervous System: Hypokinesia.

Gastrointestinal: Bilirubinemia, increased hepatic enzymes (0.2 percent of hypertension patients and 0.4 percent of heart failure patients were discontinued from therapy because of increases in hepatic enzymes) [see Adverse Reactions].

Psychiatric: Nervousness, sleep disorder, aggravated depression, impaired concentration, abnormal thinking, paroniria, emotional lability.

Respiratory System: Asthma [see Contraindications].

Reproductive, male: Decreased libido.

Skin and Appendages: Pruritus, rash erythematous, rash maculopapular, rash psoriaform, photosensitivity reaction.

Special Senses: Tinnitus.

Urinary System: Micturition frequency increased.

Autonomic Nervous System: Dry mouth, sweating increased.

Metabolic and Nutritional: Hypokalemia, hypertriglyceridemia.

Hematologic: Anemia, leukopenia.

The following events were reported in greater than 0.1 percent of patients and are potentially important:

Complete AV block, bundle branch block, myocardial ischemia, cerebrovascular disorder, convulsions, migraine, neuralgia, paresis, anaphylactoid reaction, alopecia, exfoliative dermatitis, amnesia, GI hemorrhage, bronchospasm, pulmonary edema, decreased hearing, respiratory alkalosis, increased BUN, decreased HDL, pancytopenia, and atypical lymphocytes.

#### Laboratory Abnormalities

Reversible elevations in serum transaminases (ALT or AST) have been observed during treatment with COREG. Rates of transaminase elevations (2- to 3-times the upper limit of normal) observed during controlled clinical trials have generally been similar between patients treated with COREG and those treated with placebo. However, transaminase elevations, confirmed by rechallenge, have been observed with COREG. In a long-term, placebo-controlled trial in severe heart failure, patients treated with COREG had lower values for hepatic transaminases than patients treated with placebo, possibly because improvements in cardiac function induced by COREG led to less hepatic congestion and/or improved hepatic blood flow.

#### Postmarketing Experience

The following adverse reactions have been identified during post-approval use of COREG. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Reports of aplastic anemia and severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme) have been rare and received only when carvedilol was

administered concomitantly with other medications associated with such reactions. Rare reports of hypersensitivity reactions (e.g., anaphylactic reaction, angioedema, and urticaria) have been received for COREG and COREG CR, including cases occurring after the initiation of COREG CR in patients previously treated with COREG. Urinary incontinence in women (which resolved upon discontinuation of the medication) and interstitial pneumonitis have been reported rarely.

## **OVERDOSAGE**

Overdosage may cause severe hypotension, bradycardia, cardiac insufficiency, cardiogenic shock, and cardiac arrest. Respiratory problems, bronchospasms, vomiting, lapses of consciousness, and generalized seizures may also occur.

The patient should be placed in a supine position and, where necessary, kept under observation and treated under intensive-care conditions. Gastric lavage or pharmacologically induced emesis may be used shortly after ingestion. The following agents may be administered:

for excessive bradycardia: Atropine, 2 mg IV.

If peripheral vasodilation dominates, it may be necessary to administer adrenaline or noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant bradycardia, pacemaker therapy should be performed. For bronchospasm, (as aerosol or IV) or aminophylline IV should be given. In the event of seizures, slow IV injection of diazepam or clonazepam is recommended.

NOTE: In the event of severe intoxication where there are symptoms of shock, treatment with antidotes must be continued for a sufficiently long period of time consistent with the 7- to 10-hour half-life of carvedilol.

Cases of overdosage with COREG alone or in combination with other drugs have been reported.

Quantities ingested in some cases exceeded 1,000 milligrams. Symptoms experienced included low blood pressure and heart rate. Standard supportive treatment was provided and individuals recovered.

## **DOSAGE & ADMINISTRATION**

COREG should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

### **Heart Failure**

#### **DOSAGE MUST BE INDIVIDUALIZED AND CLOSELY MONITORED BY A PHYSICIAN**

**DURING UP-TITRATION.** Prior to initiation of COREG, it is recommended that fluid retention be minimized. The recommended starting dose of COREG is 3.125 mg twice daily for 2 weeks. If tolerated, patients may have their dose increased to 6.25, 12.5, and 25 mg twice daily over successive intervals of at least 2 weeks. Patients should be maintained on lower doses if higher doses are not tolerated. A maximum dose of 50 mg twice daily has been administered to patients with mild-to-moderate heart failure weighing over 85 kg (187 lbs).

Patients should be advised that initiation of treatment and (to a lesser extent) dosage increases may be associated with transient symptoms of dizziness or lightheadedness (and rarely syncope) within the first hour after dosing. During these periods, patients should avoid situations such as driving or hazardous tasks, where symptoms could result in injury. Vasodilatory symptoms often do not require treatment, but it may be useful to separate the time of dosing of COREG from that of the ACE inhibitor or to reduce temporarily the dose of the ACE inhibitor. The dose of COREG should not be increased until symptoms of worsening heart failure or vasodilation have been stabilized.

Fluid retention (with or without transient worsening heart failure symptoms) should be treated by an increase in the dose of diuretics.

The dose of COREG should be reduced if patients experience bradycardia (heart rate greater than 55 beats/minute).

Episodes of dizziness or fluid retention during initiation of COREG can generally be managed without discontinuation of treatment and do not preclude subsequent successful titration of, or a favorable response to, carvedilol.

### **Left Ventricular Dysfunction Following Myocardial Infarction**

**DOSAGE MUST BE INDIVIDUALIZED AND MONITORED DURING UP-TITRATION.** Treatment with COREG may be started as an inpatient or outpatient and should be started after the patient is hemodynamically stable and fluid retention has been minimized. It is recommended that COREG be started at 6.25 mg twice daily and increased after 3 to 10 days, based on tolerability, to 12.5 mg twice daily, then again to the target dose of 25 mg twice daily. A lower starting dose may be used (3.125 mg twice daily) and/or the rate of up-titration may be slowed if clinically indicated (e.g., due to low blood pressure or heart rate, or fluid retention). Patients should be maintained on lower doses if higher doses are not tolerated. The recommended dosing regimen need not be altered in patients who received treatment with an IV or oral during the acute phase of the myocardial infarction.

### **Hypertension**

**DOSAGE MUST BE INDIVIDUALIZED.** The recommended starting dose of COREG is 6.25 mg twice daily. If this dose is tolerated, using standing systolic pressure measured about 1 hour after dosing as a guide, the dose should be maintained for 7 to 14 days, and then increased to 12.5 mg twice daily if needed, based on trough blood pressure, again using standing systolic pressure one hour after

dosing as a guide for tolerance. This dose should also be maintained for 7 to 14 days and can then be adjusted upward to 25 mg twice daily if tolerated and needed. The full antihypertensive effect of COREG is seen within 7 to 14 days. Total daily dose should not exceed 50 mg.

Concomitant administration with a diuretic can be expected to produce additive effects and exaggerate the orthostatic component of carvedilol action.

#### Hepatic Impairment

COREG should not be given to patients with severe hepatic impairment [see Contraindications].

## DOSAGE FORMS & STRENGTHS

The white, oval, film-coated tablets are available in the following strengths: 3.125 mg engraved with 39 and SB, 6.25 mg engraved with 4140 and SB, 12.5 mg engraved with 4141 and SB, and 25 mg engraved with 4142 and SB.

## HOW SUPPLIED

Manufacturer by Dr.Reddy's Laboratories Inc.

Carvedilol 25mg tablets are round, yellow with a imprints of R 255

Store below 30(86Protect from moisture. Dispense in a tight, light-resistant container.

## INFORMATION FOR PATIENTS

### PATIENT INFORMATION

#### COREG (Co-REG)

#### Carvedilol Tablets

Read the Patient Information that comes with COREG before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about COREG, ask your doctor or pharmacist.

#### What is COREG?

COREG is a prescription medicine that belongs to a group of medicines called beta-blockers. COREG is used, often with other medicines, for the following conditions:

- To treat patients with high blood pressure (hypertension)
- To treat patients who had a heart attack that worsened how well the heart pumps
- To treat patients with certain types of heart failure
- 

COREG is not approved for use in children under 18 years of age.

#### Who should not take COREG?

Do not take COREG if you:

Have severe heart failure and are hospitalized in the intensive care unit or require certain intravenous medications that help support circulation (inotropic medications)

- Are prone to asthma or other breathing problems
- Have a slow heartbeat or a heart that skips a beat (irregular heartbeat)
- Have liver problems
- Are allergic to any of the ingredients in COREG. The active ingredient is carvedilol. See the end of this leaflet for a list of all the ingredients in COREG.
- 

#### What should I tell my doctor before taking COREG?

Tell your doctor about all of your medical conditions, including if you:

Have asthma or other lung problems (such as bronchitis or emphysema)

- Have problems with blood flow in your feet and legs (peripheral vascular disease) COREG can make some of your symptoms worse.

- Have diabetes
- Have thyroid problems
- Have a condition called pheochromocytoma
- Have had severe allergic reactions
- Are pregnant or trying to become pregnant. It is not known if COREG is safe for your unborn baby. You and your doctor should talk about the best way to control your high blood pressure during pregnancy.
- Are breastfeeding. It is not known if COREG passes into your breast milk. You should not breastfeed while using COREG.
- Are scheduled for surgery and will be given anesthetic agents
- Are taking prescription or non-prescription medicines, vitamins, and herbal supplements. COREG and certain other medicines can affect each other and cause serious side effects. COREG may affect the way other medicines work. Also, other medicines may affect how well COREG works.

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Keep a list of all the medicines you take. Show this list to your doctor and pharmacist before you start a new medicine.

How should I take COREG?

It is important for you to take your medicine every day as directed by your doctor. If you stop taking COREG suddenly, you could have chest pain and/or a heart attack. If your doctor decides that you should stop taking COREG, your doctor may slowly lower your dose over a period of time before stopping it completely.

Take COREG exactly as prescribed. Your doctor will tell you how many tablets to take and how often. In order to minimize possible side effects, your doctor might begin with a low dose and then slowly increase the dose.

- Do not stop taking COREG and do not change the amount of COREG you take without talking to your doctor.
- Tell your doctor if you gain weight or have trouble breathing while taking COREG.
- Take COREG with food.
- If you miss a dose of COREG, take your dose as soon as you remember, unless it is time to take your next dose. Take your next dose at the usual time. Do not take 2 doses at the same time.
- If you take too much COREG, call your doctor or poison control center right away.

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What should I avoid while taking COREG?

COREG can cause you to feel dizzy, tired, or faint. Do not drive a car, use machinery, or do anything that needs you to be alert if you have these symptoms.

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What are possible side effects of COREG?

Low blood pressure (which may cause dizziness or fainting when you stand up). If these happen, sit or lie down right away and tell your doctor.

- Tiredness. If you feel tired or dizzy you should not drive, use machinery, or do anything that needs you to be alert.
- Slow heartbeat.
- Changes in your blood sugar. If you have diabetes, tell your doctor if you have any changes in your blood sugar levels.
- COREG may hide some of the symptoms of low blood sugar, especially a fast heartbeat.
- COREG may mask the symptoms of hyperthyroidism (overactive thyroid).

- Worsening of severe allergic reactions.
- Rare but serious allergic reactions (including hives or swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing) have happened in patients who were on COREG. These reactions can be life-threatening.

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Other side effects of COREG include shortness of breath, weight gain, diarrhea, and fewer tears or dry eyes that become bothersome if you wear contact lenses.

Call your doctor if you have any side effects that bother you or don't go away.

How should I store COREG?

Store COREG at less than 86°F (30°F). Keep the tablets dry.

- Safely, throw away COREG that is out of date or no longer needed.
- Keep COREG and all medicines out of the reach of children.

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General Information about COREG

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use COREG for a condition for which it was not prescribed. Do not give COREG to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about COREG. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about COREG that is written for healthcare professionals. You can also find out more about COREG by visiting the website [www.COREG.com](http://www.COREG.com) or calling 1-888-825-5249. This call is free.

#### **PACKAGE LABEL-PRINCIPAL DISPLAY PANEL SECTION**

DRUG: Carvedilol

GENERIC: Carvedilol

DOSAGE: TABLET

ADMINISTRATION: ORAL

NDC: 49349-032-02

STRENGTH: 3.125 mg

COLOR: yellow

SHAPE: ROUND

SCORE: No score

SIZE: 5 mm

IMPRINT: 30

QTY: 30

**CARVEDILOL**

**3.125MG TAB**

**QTY: 00030**

**NDC#: 49349-0032-02 INT:tb ID#:R 252**

**EXPIRES: COL: YELLOW SHAPE: ROUND**

**LOT#: 012345**

**DIST: DR.REDDY'S LABS BACHEPALLI 502325 INDIA**

**MFG: DR.REDDY'S LABS BACHEPALLI 502325 INDIA**

A. Caution Federal law prohibits transfer of this drug to any person other than for whom it was prescribed.

B. Store at a temperature between 15 degree C and 30 degree C (59 degree F and 86 degree F) (see USP)

C. Re-packaged by: RemedyRepack Inc. 655 Kolter Dr.,  
Indiana, PA 15701, 1-724-465-8762



CARVEDILOL				
carvedilol tablet				
Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:49349-032(NDC:55111-252)	
Route of Administration	ORAL	DEA Schedule		
Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
CARVEDILOL (UNII: 0K47UL67F2) (CARVEDILOL - UNII:0K47UL67F2)		CARVEDILOL	3.125 mg	
Inactive Ingredients				
Ingredient Name			Strength	
HYDRATED SILICA (UNII: Y6O7T4G8P9)				
CROSPOLVIDONE (UNII: 68401960MK)				
HYDROMELLOSES (UNII: 3NXW29V3WO)				
.BETA.-D-GALACTOSE (UNII: RQ6K52J67A)				
MAGNESIUM STEARATE (UNII: 70097M6130)				
AMMONIUM LAURETH-5 SULFATE (UNII: 43ZIH89148)				
POLYSORBATE 80 (UNII: 6OZP39ZG8H)				
COPOLVIDONE (UNII: D9C330MD8B)				
Product Characteristics				
Color	yellow	Score	no score	
Shape	ROUND (TABLET)	Size	5mm	
Flavor		Imprint Code	R;252	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49349-032-02	30 in 1 BLISTER PACK		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA076649	08/02/2011		

Labeler - REMEDYREPACK INC. (829572556)